

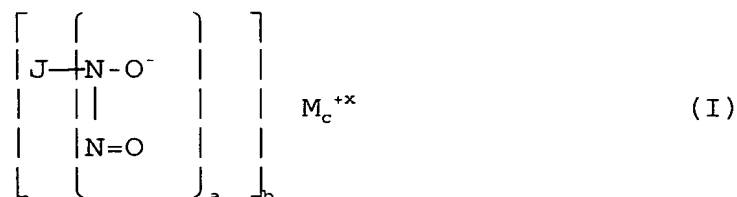
PENDING CLAIMS

U.S. SERIAL NO. 08/837,812

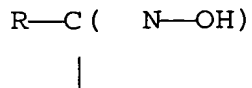
BIOPOLYMER-BOUND NITRIC OXIDE-RELEASING COMPOSITIONS, PHARMACEUTICAL COMPOSTIONS INCORPORATING SAME AND METHODS OF TREATING BIOLOGICAL DISORDERS USING SAME

1. A polymeric composition capable of releasing nitric oxide, said composition comprising (i) a biopolymeric backbone wherein said backbone is of an oligonucleotide, a nucleic acid, a tissue-specific antibody or fragment thereof, a cell-specific antibody or fragment thereof, a tumor-specific antibody or fragment thereof, a protein containing a recognition sequence for a receptor-ligand interaction favorable to tumor cell attachment, an anti-chemotactic agent, or a hormone, and (ii) at least one nitric oxide-releasing $N_2O_2^-$ functional group selected from the group consisting of $X\{N(O)NO\}$ and $[N(O)NO\}X$, wherein X is an organic moiety covalently bonded to said $[N_2O_2]$, and wherein the $[N_2O_2]$ group is covalently bonded in said polymeric composition through said organic moiety X.

5. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



wherein J is an inorganic moiety or an organic moiety selected from the group consisting of C_1 - C_{12} aliphatic, C_3 - C_8 cycloalkyl, benzyl, phenyl, substituted benzyl, substituted phenyl, benzylcarbonyl, phenylcarbonyl, substituted benzylcarbonyl, substituted phenylcarbonyl, C_1 - C_{12} acyl, and

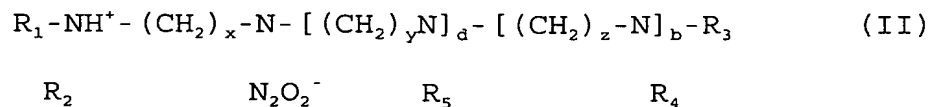


wherein R is C₁-C₁₂ aliphatic, C₃-C₈ cycloalkyl, benzyl, phenyl, substituted benzyl or substituted phenyl, and said substituted benzyl and substituted phenyl is substituted with one or two substituents selected from the group consisting of halogen, hydroxy, C₁-C₄ alkyl, C₁-C₄ alkoxy, amino, mono C₁-C₄ alkylamino, di C₁-C₄ alkyl-amino, phenyl and phenoxy, M^{+x} is a pharmaceutically acceptable cation, where x is the valence of the cation, a is one or two, and b and c are the smallest integers that result in a neutral compound.

6. The method of claim 5, wherein J is a moiety which is linked to the nitrogen of the remainder of the complex through an atom other than a carbon atom.

7. The polymeric composition of claim 5, wherein the nitric-oxide releasing group is a compound other than a salt of alanosine or dopastin.

8. The polymeric composition of claim 1, wherein said nitric oxide-releasing N₂O₂⁻ functional group is of the formula:

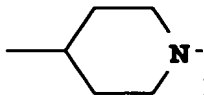



wherein b and d are the same or different and may be zero or one, R₁, R₂, R₃, R₄, and R₅ are the same or different and may be

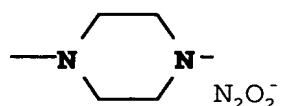
hydrogen, C₃₋₈ cycloalkyl, C₁₋₁₂ straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluyyl, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, and x, y, and z are the same or different and are integers from 2 to 12.

9. The polymeric composition of claim 1, wherein said nitric oxide-releasing N₂O₂⁻ functional group is of the formula:



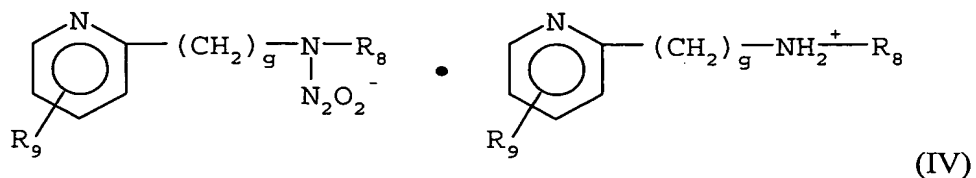
wherein B is  or ,

R₆ and R₇ are the same or different and may be hydrogen, C₃₋₈ cycloalkyl, C₁₋₁₂ straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluyyl, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, f is an integer from 0 to 12, with the proviso that when B is the substituted piperazine moiety



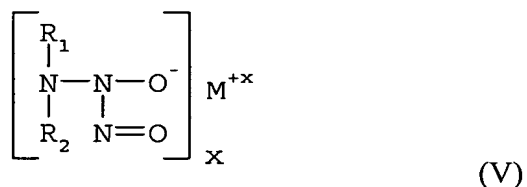
then f is an integer from 2 to 12.

10. The polymeric composition of claim 1, wherein said nitric oxide-releasing N_2O_2^- functional group is of the formula:



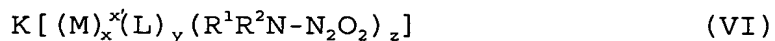
wherein R_8 is hydrogen, C_{3-8} cycloalkyl, C_{1-12} straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluyyl, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, R_9 is hydrogen or a $\text{C}_1\text{-C}_{12}$ straight or branched chain alkyl, and g is 2 to 6.

11. The polymeric composition of claim 1, wherein said nitric oxide-releasing N_2O_2^- functional group is of the formula:



wherein R_1 and R_2 are independently selected from the group consisting of a straight chain or branched chain $\text{C}_1 - \text{C}_{12}$ alkyl group and a benzyl group, or else R_1 and R_2 together with the nitrogen atom they are bonded to form a heterocyclic group, a pyrrolidino, piperidino, piperazino or morpholino group, $\text{M}^{+\text{x}}$ is a pharmaceutically acceptable cation, and x is the valence of the cation.

12. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



wherein M is a pharmaceutically acceptable metal, or, where x is at least two, a mixture of two different pharmaceutically acceptable metals, L is a ligand different from $(R^1R^2N-N_2O_2)$ and is bound to at least one metal, R^1 and R^2 are each organic moieties and may be the same or different, x is an integer of from 1 to 10, x' is the formal oxidation state of the metal M, and is an integer of from 1 to 6, y is an integer of from 1 to 18, and where y is at least 2, the ligands L may be the same or different, z is an integer of from 1 to 20, and K is a pharmaceutically acceptable counterion to render the compound neutral to the extent necessary.

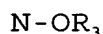
13. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



wherein R is C_{2-8} lower alkyl, phenyl, benzyl, or C_{3-8} cycloalkyl, any of which R groups may be substituted by one to three substituents, which are the same or different, selected from the group consisting of halo, hydroxy, C_{1-8} alkoxy, $-NH_2$, $-C(O)NH_2$, $-CH(O)$, $-C(O)OH$, and $-NO_2$, X is a pharmaceutically acceptable cation, a pharmaceutically acceptable metal center, or a pharmaceutically acceptable organic group selected from the group consisting of C_{1-8} lower

alkyl, $-C(O)CH_3$, and $-C(O)NH_2$, and y is one to three, consistent with the valence of X .

14. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



wherein R_1 and R_2 are independently chosen from C_{1-12} straight chain alkyl, C_{1-12} alkoxy or acyloxy substituted straight chain alkyl, C_{2-12} hydroxy or halo substituted straight chain alkyl, C_{3-12} branched chain alkyl, C_{3-12} hydroxy, halo, alkoxy, or acyloxy substituted branched chain alkyl, C_{3-12} straight chain olefinic and C_{3-12} branched chain olefinic which are unsubstituted or substituted with hydroxy, alkoxy, acyloxy, halo or benzyl, or R_1 and R_2 together with the nitrogen atom to which they are bonded form a heterocyclic group, a pyrrolidino, piperidino, piperazino or morpholino group, and R_3 is a group selected from C_{1-12} straight chain and C_{3-12} branched chain alkyl which are unsubstituted or substituted by hydroxy, halo, acyloxy or alkoxy, C_{2-12} straight chain or C_{3-12} branched chain olefinic which are unsubstituted or substituted by halo, alkoxy, acyloxy or hydroxy, C_{1-12} unsubstituted or substituted acyl, sulfonyl and carboxamido; or R_3 is a group of the formula $-(CH_2)_n-ON=N(O)NR_1R_2$, wherein n is an integer of 2-8, and R_1 and R_2 are as defined above; with the proviso that R_1 , R_2 and R_3 do not contain a halo or a hydroxy substituent α to a heteroatom.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 1.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 5.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 6.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 7.

22. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 8.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 9.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 10.

25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 11.

26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 12.

27. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering to said mammal a polymeric composition capable of releasing nitric oxide, said composition comprising a biopolymeric backbone wherein said backbone is of a protein and a nitric oxide-releasing N_2O_2 - functional group bound to said biopolymer, in an amount sufficient to release a therapeutically effective amount of nitric oxide.

31. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 5 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

32. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 6 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

33. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 7 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

34. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 8 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

35. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 9 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

36. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 10 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

37. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 11 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

38. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 12 in an amount sufficient to release a therapeutically effective amount of nitric oxide.